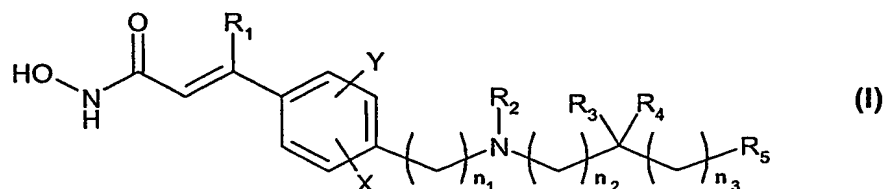


What is claimed is:

1. A combination comprising
 - (a) death receptor ligand, and
 - (b) a histone deacetylase inhibitor of formula (I)



wherein

R₁ is H; halo; or a straight-chain C₁-C₆alkyl, especially methyl, ethyl or *n*-propyl, which methyl, ethyl and *n*-propyl substituents are unsubstituted or substituted by one or more substituents described below for alkyl substituents;

R₂ is selected from H; C₁-C₁₀alkyl, preferably C₁-C₆alkyl, e.g., methyl, ethyl or -CH₂CH₂-OH; C₄-C₉cycloalkyl; C₄-C₉heterocycloalkyl; C₄-C₉heterocycloalkylalkyl; cycloalkylalkyl, e.g., cyclopropylmethyl; aryl; heteroaryl; arylalkyl, e.g., benzyl; heteroarylalkyl, e.g., pyridylmethyl; -(CH₂)_nC(O)R₆; -(CH₂)_nOC(O)R₆; amino acyl; HON-C(O)-CH=C(R₁)-aryl-alkyl-; and -(CH₂)_nR₇;

R₃ and R₄ are the same or different and, independently, H; C₁-C₆alkyl; acyl; or acylamino; or

R₃ and R₄, together with the carbon to which they are bound, represent C=O, C=S or C=NR₈; or

R₂, together with the nitrogen to which it is bound, and R₃, together with the carbon to which it is bound, can form a C₄-C₉heterocycloalkyl; a heteroaryl; a polyheteroaryl; a non-aromatic polyheterocycle; or a mixed aryl and non-aryl polyheterocycle ring;

R₅ is selected from H; C₁-C₆alkyl; C₄-C₉cycloalkyl; C₄-C₉heterocycloalkyl; acyl; aryl; heteroaryl; arylalkyl, e.g., benzyl; heteroarylalkyl, e.g., pyridylmethyl; aromatic polycycles; non-aromatic polycycles; mixed aryl and non-aryl polycycles; polyheteroaryl; non-aromatic polyheterocycles; and mixed aryl and non-aryl polyheterocycles;

n, n₁, n₂ and n₃ are the same or different and independently selected from 0-6, when n₁ is 1-6, each carbon atom can be optionally and independently substituted with R₃ and/or R₄;

X and Y are the same or different and independently selected from H; halo; C₁-C₄alkyl, such as CH₃ and CF₃; NO₂; C(O)R₁; OR₉; SR₉; CN; and NR₁₀R₁₁;

R₆ is selected from H; C₁-C₆alkyl; C₄-C₉cycloalkyl; C₄-C₉heterocycloalkyl; cycloalkylalkyl, e.g., cyclopropylmethyl; aryl; heteroaryl; arylalkyl, e.g., benzyl and 2-phenylethenyl; heteroarylalkyl, e.g., pyridylmethyl; OR₁₂; and NR₁₃R₁₄;

R₇ is selected from OR₁₅; SR₁₅; S(O)R₁₆; SO₂R₁₇; NR₁₃R₁₄; and NR₁₂SO₂R₆;

R₈ is selected from H; OR₁₅; NR₁₃R₁₄; C₁-C₆alkyl; C₄-C₉cycloalkyl; C₄-C₉heterocycloalkyl; aryl; heteroaryl; arylalkyl, e.g., benzyl; and heteroarylalkyl, e.g., pyridylmethyl;

R₉ is selected from C₁-C₄alkyl, e.g., CH₃ and CF₃; C(O)-alkyl, e.g., C(O)CH₃; and C(O)CF₃;

R₁₀ and R₁₁ are the same or different and independently selected from H; C₁-C₄alkyl; and -C(O)-alkyl;

R₁₂ is selected from H; C₁-C₆alkyl; C₄-C₉cycloalkyl; C₄-C₉heterocycloalkyl; C₄-C₉heterocycloalkylalkyl; aryl; mixed aryl and non-aryl polycycle; heteroaryl; arylalkyl, e.g., benzyl; and heteroarylalkyl, e.g., pyridylmethyl;

R₁₃ and R₁₄ are the same or different and independently selected from H; C₁-C₆alkyl; C₄-C₉cycloalkyl; C₄-C₉heterocycloalkyl; aryl; heteroaryl; arylalkyl, e.g., benzyl; heteroarylalkyl, e.g., pyridylmethyl; amino acyl; or

R₁₃ and R₁₄, together with the nitrogen to which they are bound, are C₄-C₉heterocycloalkyl; heteroaryl; polyheteroaryl; non-aromatic polyheterocycle; or mixed aryl and non-aryl polyheterocycle;

R₁₅ is selected from H; C₁-C₆alkyl; C₄-C₉cycloalkyl; C₄-C₉heterocycloalkyl; aryl; heteroaryl; arylalkyl; heteroarylalkyl; and (CH₂)_mZR₁₂;

R₁₆ is selected from C₁-C₆alkyl; C₄-C₉cycloalkyl; C₄-C₉heterocycloalkyl; aryl; heteroaryl; polyheteroaryl; arylalkyl; heteroarylalkyl; and (CH₂)_mZR₁₂;

R₁₇ is selected from C₁-C₆alkyl; C₄-C₉cycloalkyl; C₄-C₉heterocycloalkyl; aryl; aromatic polycycles; heteroaryl; arylalkyl; heteroarylalkyl; polyheteroaryl and NR₁₃R₁₄;

m is an integer selected from 0-6; and

Z is selected from O; NR₁₃; S; and S(O),

or a pharmaceutically acceptable salt thereof.

2. A method for the prevention or treatment of proliferative diseases, in a mammal, which comprises treating the mammal with pharmaceutically effective amounts of a combination of:
 - (a) death receptor ligand, and
 - (b) a histone deacetylase inhibitor of formula (I) according to claim 1.
3. The combination according to Claim 1, wherein the death receptor ligand is TRAIL, TRAIL/Apo-2L, TRAIL mimetics, agonistic antibodies, or other agents that can bind to DR4 and DR5 triggering the activity of caspase-8 and apoptosis through the assembly of a cell-membrane associated multi-protein death inducing signaling complex (DISC).
4. The combination of Claim 1, wherein the HDAC is selected from the group consisting of *N*-hydroxy-3-[4-[[2-(2-hydroxyethyl)[2-(1*H*-indol-3-yl)ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide, *N*-hydroxy-3-[4-[[2-(1*H*-indol-3-yl)ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide and *N*-hydroxy-3-[4-[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide, or a pharmaceutically acceptable salt thereof.
5. The combination of Claim 1 for the prevention or treatment of leukemia.
6. The method of Claim 2, wherein the mammal is a human.
7. The combination of Claim 1 for the prevention or treatment of acute myeloid leukemia (AML).
8. A combined preparation which comprises:
 - (a) one or more unit dosage forms of a death receptor ligand; and
 - (b) one or more unit dosage forms of a HDAC of formula (I) of Claim 1.
9. The combined preparation according to Claim 8, wherein the death receptor ligand is TRAIL, TRAIL/Apo-2L, TRAIL mimetics, agonistic antibodies, or other agents that can bind to DR4 and DR5 triggering the activity of caspase-8 and apoptosis through the assembly of a cell-membrane associated multi-protein DISC.
10. The combined preparation of Claim 9, wherein the histone deacetylase inhibitor is selected from the group consisting of *N*-hydroxy-3-[4-[[2-(2-hydroxyethyl)[2-(1*H*-indol-3-

yl)ethyl]-amino)methyl]phenyl]-2*E*-2-propenamide, *N*-hydroxy-3-[4-[[[2-(1*H*-indol-3-yl)ethyl]-amino)methyl]phenyl]-2*E*-2-propenamide and *N*-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino)methyl]phenyl]-2*E*-2-propenamide, or a pharmaceutically acceptable salt thereof.

11. A method of treating or preventing premalignant proliferative diseases in a mammal which comprises treating the mammal with a combination of:

- (a) a pharmaceutically effective amount of a death receptor ligand; and
- (b) a pharmaceutically effective amount of *N*-hydroxy-3-[4-[[[2-(2-hydroxyethyl)[2-(1*H*-indol-3-yl)ethyl]-amino)methyl]phenyl]-2*E*-2-propenamide, *N*-hydroxy-3-[4-[[[2-(1*H*-indol-3-yl)ethyl]-amino)methyl]phenyl]-2*E*-2-propenamide or *N*-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino)methyl]phenyl]-2*E*-2-propenamide; or a pharmaceutically effective salt thereof.

12. The method according to Claim 11, wherein the death receptor ligand is TRAIL, TRAIL/Apo-2L, TRAIL mimetics, agonistic antibodies, or other agents that can bind to DR4 and DR5 triggering the activity of caspase-8 and apoptosis through the assembly of a cell-membrane associated multi-protein DISC.

13. A method of treating or preventing proliferative diseases in a mammal which comprises treating the mammal with a combination of:

- (a) a pharmaceutically effective amount of a death receptor ligand; and
- (b) a pharmaceutically effective amount of an HDAI.

14. A combined preparation which comprises:

- (a) one or more unit dosage forms of a death receptor ligand; and
- (b) one or more unit dosage forms of a HDAI.